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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,169	12/09/2005	Kazumi Danjo	Q91343	9404

23373 7590 03/04/2010

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EXAMINER	
GREENE, IVAN A	
ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
03/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,169	DANJO ET AL.	
	Examiner	Art Unit	
	IVAN GREENE	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,13,14,17 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *13,14 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 4, 8, 13, 14, 17 and 20-22 are currently pending. The restriction dated 09/25/2008 is still in place and claims 13, 14 and 17 stand withdrawn. Claims 4, 8 and 20-22 are being examined on the merits.

The examiner acknowledges applicant's request to have the filing date of the drawings confirmed. The examiner confirms the filing date of the accepted drawings is December 9th 2005, as indicated in the instant office action summary (attached).

Claim Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

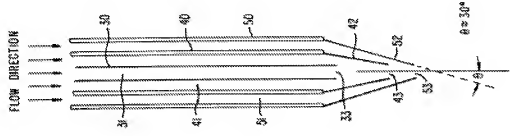
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 4 and 8 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by HANNA (US 6,063,138, as previously cited).

Disclosure of the Prior Art

HANNA discloses a method and apparatus for the formation of particles which allows for a high degree of control over the size, shape, crystalline form and other physico-chemical properties (abstract). HANNA further discloses lactose is commonly used as a carrier for pharmaceuticals, in particular for drugs delivered by inhalation (3:2-5). HANNA further discloses Example 1 in which a solution of lactose in a relatively small amount of water and a relatively large amount of a second vehicle, methanol was

co-introduced, with supercritical CO_2, into the particle formation vessel (19:1-31). The particle formation vessel used is shown in figure 1 and the nozzle used is shown in figure 3 (reproduced below for convenience) which includes an inner passage 31, and intermediate passage 41, and an outer passage 51. The fluids are co-introduced through the nozzle such that the first vehicle (lactose solution) is introduced through the inner passage 31, the second vehicle (methanol) is introduced through the intermediate passage 41, and the supercritical fluid (carbon dioxide) is introduced through the outer passage 51 (15:15-19). The mixing of the solution or suspension and the second vehicle then occurs immediately prior to their dispersion by the supercritical fluid between orifices 43 and 53 (15:19-22).



HANNA discloses Example 3 (prepared using the method discussed above) in which a solution of maltose was dissolved in water, the second vehicle is ethanol and the supercritical fluid is carbon dioxide (19:63-67; 20:1-5, 28-37). And similarly, HANNA discloses Example 4 (prepared using the method discussed above) in which a solution of trehalose ([a sugar]) was dissolved in water, the second vehicle is ethanol and the supercritical fluid is carbon dioxide (20:47-60).

The above examples are considered to anticipate the instantly rejected claims because the specification provides a definition of "A radial spherical crystallization product" as follows:

> [0023] The radial spherical crystallization product of the present invention is a crystallization product comprising needle-shaped projections radially extending from the core to form a spherical configuration (refer to **FIGS. 1 and 2**). Other ways to describe this configuration include reference to an echinoid, chestnut bur, or spherical moss (*Cladophora sauteri*) covered with a spherical shell with long thorns projecting therefrom.

And HANNA discloses the micrograph of the product of Example 1 as follows:

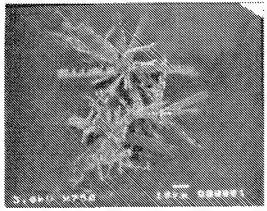


FIG. 5

Which micrograph is "a crystallization product comprising needle-shaped projections radially extending from the core to form a spherical configuration" (as defined by applicant).

It is further noted that, while the structure of the crystallization product of HANNA is not coextensive with Applicant's crystallization product (as shown in figures 1 and 2), the claims (as currently recited) are not considered to be limited to the structure of the

product shown in figures 1 and 2 of the instant specification because the scope of the instantly rejected claims embraces other crystalline forms.

With regard to the process steps of claim 4, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP § 2113.

2. Claim 4 remains rejected under 35 U.S.C. 102(b) as being anticipated by REVERCHON (Powder Technol., 114, pp. 17-22, as previously cited).

REVERCHON discloses the micronization of salbutamol by supercritical antisolvent (SAS) precipitation (abstract). REVERCHON further discloses the SAS experiments using supercritical CO2 and a pure liquid solvent with a fixed ratio of CO2/liquid solution (20:1) and fixed liquid flow rate (1 mL/min) and temperature (40°C) while pressure, solution concentration and the type of solvent used were varied one at a time (p. 18, col. 2, lines 12-17 & 50-56). REVERCHON further discloses the "star-like" crystallization product comprising salbutamol produced by SAS at 150 bar and a concentration of 10 mg/mL using a dimethylsulfoxide solvent system (p. 20, col. 2, lines 1-9; Figure 3).

The above example is considered to anticipate the instantly rejected claims because the specification provides a definition of "A radial spherical crystallization product" as follows:

> **[0023]** The radial spherical crystallization product of the present invention is a crystallization product comprising needle-shaped projections radially extending from the core to form a spherical configuration (refer to **FIGS. 1 and 2**). Other ways to describe this configuration include reference to an echinoid, chestnut bur, or spherical moss (*Cladophora sauteri*) covered with a spherical shell with long thorns projecting therefrom.

And REVERCHON discloses the micrograph of the product of the example discussed above as follows:

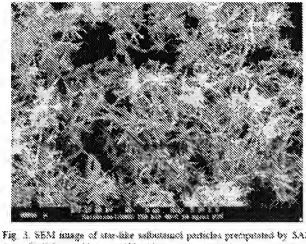


Fig. 3. SEM image of star-like salbutamol particles precipitated by SAS from DMSO at 130 bar, 40°C, 10 mg/ml. At higher concentrations, salbutamol particles tend to form more structured morphologies.

Which micrograph is "a crystallization product comprising needle-shaped projections radially extending from the core to form a spherical configuration" (as defined by applicant).

It is further noted that, while the structure of the crystallization product of REVERCHON is not coextensive with Applicant's crystallization product (as shown in figures 1 and 2), the claims (as currently recited) are not considered to be limited to the structure of the product shown in figures 1 and 2 of the instant specification because the scope of the instantly rejected claims embraces other crystalline forms.

With regard to the process steps of claim 4, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP § 2113.

Response to Arguments:

Applicant's arguments filed 02/24/2010 have been fully considered but they are not persuasive.

Applicant's argument that neither HANNA nor REVERCHON teaches each and every element of the claim 4, is not convincing because the product, as currently claimed, does not sufficiently structurally distinguish from the products described in the prior art references HANNA and REVERCHON. Claim 4 recites "A radial spherical crystallization product obtained by [the described process], however there are no "structural" limitations outside of the preamble statement. And while the preamble statement does recite the structural limitation "radial spherical crystallization product" this limitation does not sufficiently distinguish the instantly claimed invention from the disclosure of HANNA or REVERCHON because both HANNA and REVERCHON disclose a "radial spherical crystallization product." (see MPEP § 2111.02 for a discussion of preamble statements).

Applicant's argument that the presently claimed product is distinguished by the Rule 132 Declaration filed May 7, 2009 is acknowledged. In response the examiner argues that, as currently recited, independent claim does not recite sufficient "structural" limitations to distinguish over the prior art (as discussed above) therefore the Rule 132 Declaration, filed May 7, is not commensurate in scope with the independent claim.

The examiner notes that, for purposes of examination on the merits, product-by-process claims are not limited by the process steps but rather the structure that results from those steps. Product-by-process claims are examined as product claims, limited only by product structure recited in the claim. MPEP § 2113 states:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

The recited structure of claim 4, "A radial spherical crystallization product" is met by HANNA and REVERCHON because they both recite such a product (discussed above). The process of making the radial spherical products of HANNA and REVERCHON may not be exactly the same as the process of the instantly claimed invention, however the resulting product, as limited by the claim language is. In order to distinguish over the cited prior art applicant should amend the claim(s) to recite "structural limitations" such that the products disclosed by the prior art do not have the same structure.

Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 4, 8 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over HANNA (US 6,063,18, as previously cited) and REVERCHON (Powder Technol., 114, pp. 17-21, as previously cited) in view of YIANNESKIS (US 5,975,076, as previously cited) and SZABO (Journal of Crystal Growth, Vols. 237-239, Part 3, pp.2240-2245, new reference).

Applicants Claims

Applicant claims a radial spherical crystallization product obtained by emitting a mixture of carbon dioxide and ethanol and a solution comprising a sample component into a crystallization vessel through different flow channels to cause them to come in contact with each other as they are emitted into the crystallization vessel, wherein the sample component is a drug carrier, and wherein (i) the flow rate of ethanol is ¼ of the flow rate of carbon dioxide, (ii) the mixture of carbon dioxide and ethanol is a poor

solvent for the sample component, and (iii) a nozzle used to emit the mixture of carbon dioxide and ethanol, and the solution comprising the sample component is a V-shaped nozzle. Applicant further claims the radial spherical crystallization product wherein the drug carrier is a sugar or sugar alcohol. Applicant further claims a dry powder inhaler comprising the radial spherical crystallization product mixed with a pharmaceutical drug.

Determination of the scope and

content of the prior art (MPEP 2141.01)

HANNA teaches a method and apparatus for the formation of particles which allows for a high degree of control over the size, shape, crystalline form and other physico-chemical properties, as discussed above (abstract).

HANNA further teaches the substance used in the invention may be any substance which needs to be produced in particle form, for example lactose and other sugars, proteins, hydrophilic enzymes and inorganic materials (6:29-31, 36-38). HANNA further teaches the substance from which particles are formed is for use in, or as, a pharmaceutical (6:41-43). HANNA further teaches the substance may be a single or multicomponent form (6:50-54). HANNA further teaches the supercritical fluid may be any supercritical fluid (6:66-67) and may contain one or more modifiers such as methanol, ethanol, isopropanol, or acetone among others (7:7-9). HANNA further teaches the control of parameters such as size, size distribution, shape and crystalline form in the particulate product will be dependent upon the operating conditions used when carrying out the method of the invention (9:64-67) and in particular the flow rates of the supercritical fluid and/or the solution or suspension and/or the second vehicle,

into the particle formation vessel may be controlled so as to achieve a desired particle size, size distribution, shape and/or form (10:29-32). HANNA further teaches the examples 1 & 2 using lactose, example 3 using maltose, example 4 using trehalose, example 5 using sucrose, example 6 using salmeterol xinafoate, and example 7 using the protein R-TEM beta-lactamase (see Examples columns 19-21).

REVERCHON teaches aerosol drug delivery represents a valuable route to deliver many therapeutic agent, as discussed above (p. 17, col. 1, lines 1-2).

REVERCHON further teaches the micronization of salbutamol by supercritical antisolvent (SAS) precipitation (abstract). REVERCHON further teaches the SAS experiments using supercritical CO2 and a pure liquid solvent with a fixed ratio of CO2/liquid solution (20:1) and fixed liquid flow rate (1 mL/min) and temperature (40°C) while pressure, solution concentration and the type of solvent used were varied one at a time (p. 18, col. 2, lines 12-17 & 50-56). REVERCHON further teaches the radial spherical crystallization product comprising salbutamol produced by SAS at 150 bar and a concentration of 10 mg/mL using a dimethylsulfoxide solvent system (p. 20, col. 2, lines 1-9; Figure 3).

Ascertainment of the difference between

the prior art and the claims (MPEP 2141.02)

The difference between the rejected claims and the teachings of HANNA/REVERCHON is that HANNA/REVERCHON do not expressly teach a dry powder inhaler comprising a radial spherical crystallization product. This deficiency in a

dry powder inhaler is cured by the teachings of YIANNESKIS. SZABO teaches the consequences of crystal habit modification.

YIANNESKIS teaches salbutamol sulfate/lactose particles were for use in an dry powder inhaler (abstract; col. 5, lines 25-30).

SZABO teaches crystal growth of drug materials by spherical crystallization (title). SZABO further teaches the production of spherical crystal agglomerates (which is one possibility of crystal size growth) has recently gained great attention and importance due to the fact that the crystal habit can be modified during the crystallization process (p. 2240, col. 1, lines 1-6). SZABO further teaches the consequences of such modifications in the crystal habit, certain parameters can also be changed: bulk density, flow property, compactibility, cohesivity, dissolution rate, stability, etc. (p. 2240, col. 1, lines 7-10). SZABO further teaches the drug materials produced by the spherical crystallization technique result in the economical process in the development of the solid dosage forms (p. 2240, col. 2, lines 12-15).

With regard to the process steps of claim 4, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP § 2113.

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine YIANNESKIS with HANNA and REVERCHON and produce the instantly claimed invention because, as suggested by HANNA, the radial spherical crystallization product would provide for a more efficient delivery of drug substance where the desired particle size, size distribution, shape and form can be controlled. The skilled artisan would have been motivated to YIANNESKIS with HANNA and REVERCHON and produce the instantly claimed invention because the improved drug delivery product would have been especially useful when used with a suitable inhaler device. And, as suggested by SZABO, the modification of the crystal habit would result in a change of parameters such as bulk density and flow properties. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made that properties, such as bulk density and "flow-ability," could be affected by the crystal habit and thus the skilled artisan would have been motivated to optimize the crystal habit to produce the best properties for the intended application (e.g. an inhalable pharmaceutical powder).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments:

Applicant's arguments filed 02/24/2010 have been fully considered but they are not persuasive.

Applicant's arguments regarding the 103(a) rejection are primarily directed toward HANNA and REVERCHERON and have been addressed above.

Conclusion

Claims 4, 8 and 20-22 have been examined on the merits. Claims 4 and 8 are rejected under 35 U.S.C. 102(b); claims 4, 8 and 20-22 are rejected under 35 U.S.C. 103(a). No claims allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IVAN GREENE whose telephone number is (571)270-5868. The examiner can normally be reached on Monday through Thursday 7AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bonnie Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

IVAN GREENE
Examiner, Art Unit 1619

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619